UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF NEW YORK

GREGORY A. AMOS, in his capacity as Administrator of the Estate of ANDREA R. AMOS, Deceased, Plaintiff, v. BIOGEN INC. and ELAN PHARMACEUTICALS, LLC Defendants.	Civil Action Number: 13-CV-06375-MAT

MEMORANDUM OF LAW IN SUPPORT OF
DEFENDANTS' JOINT MOTION FOR SUMMARY JUDGMENT

Respectfully submitted,

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I. INTRODUCTION

Defendants[1/] Biogen Inc. and Elan Pharmaceuticals, LLC are entitled to summary judgment in this prescription drug product liability action. Plaintiff, in his capacity as administrator of the estate of his deceased wife, Andrea Amos, asserts multiple claims based on an alleged failure to adequately warn about the risk of developing a viral brain infection, "PML,"[2/] while being treated with the drug Tysabri. PML is a known and disclosed risk of Tysabri, an FDA-approved biologic drug used to treat multiple sclerosis ("MS"). Throughout Mrs. Amos's nearly five-year Tysabri treatment, the risk of PML was disclosed in Tysabri's labeling in a "black box" warning, FDA's strongest possible warning.

The undisputed summary judgment record establishes that there are no genuine issues of material fact and that Biogen and Elan are entitled to summary judgment as a matter of law. Fed. R. Civ. P. 56. Plaintiff has failed to adduce any evidence that Tysabri's black box PML warning and related warnings in Tysabri's labeling were inadequate. In fact, two courts in Tysabri cases have held recently, on an identical FDA regulatory record, that Tysabri's PML warnings were adequate as a matter of law. *Christison v. Biogen Idec Inc. and Elan Pharm., LLC*, No. 2:11-cv-01140-DN-DBP, 2016 U.S. Dist. LEXIS 110273 (D. Utah Aug. 5, 2016) (granting summary judgment to Biogen and Elan on a failure to warn claim and all other claims); *Gentile v. Biogen*

1/ "Defendants" refers to both Biogen and Elan when the legal argument is not affected by the role of the individual Defendants. Where the role of the individual Defendants has a bearing on the legal argument, the individual Defendant has been identified. Biogen and Elan collaborated on aspects of the research, development and commercialization of Tysabri. Biogen manufactured the drug, held the FDA license, and had regulatory responsibility for the drug in the United States, and was principally responsible for marketing the drug for MS in the United States. Elan distributed the drug in the United States and also had principal responsibility for the marketing of Tysabri for Crohn's disease, another approved indication for the drug. Elan was also the license holder for the drug in Europe. (SF ¶ 6).

2/ PML refers to Progressive Multifocal Leukoencephalopathy, a viral brain infection caused by the JC virus ("JCV").

Idec Inc. and Elan Pharmaceuticals, LLC, No. 1181 CV 03500, 2016 Mass. Super. LEXIS 238 (Mass. Sup. Ct. July 25, 2016) (same).

Plaintiff has not offered any expert testimony whatsoever in support of his claim that the extensive PML warnings were inadequate. Plaintiff also has not offered any competent expert testimony supporting the assertion that Defendants could have developed and "commercialized" a separate non-drug product (a JC virus antibody assay) for use with their FDA-approved drug.

In addition, Plaintiff cannot on this record establish the essential element of proximate cause because there is no evidence that any of the alleged inadequacies in the labeling would have changed Mrs. Amos's neurologists' prescribing decisions. To the contrary, the undisputed evidence establishes that her prescribing physicians knew about and considered all three of the PML risk factors which form the bases of Plaintiff's claims, and that they still decided to prescribe Tysabri to Mrs. Amos.

Finally, federal law preempts Plaintiff's claim that Defendants should have warned earlier about the significance of the presence of anti-JCV antibodies (*i.e.*, antibodies produced by the immune system to defend against JCV infection). In September 2010, Biogen proposed to FDA's Center for Drug Evaluation and Research ("CDER") warning language concerning the significance of anti-JCV antibodies as determined by a related Biogen-developed assay (a blood test). In November 2010, Biogen proposed to FDA's Center for Devices and Radiological Health ("CDRH") that Biogen should be permitted to make the assay available to Tysabri prescribers as a "laboratory developed test" ("LDT").[3/] Both FDA's CDER and CDRH divisions rejected Biogen's proposals, concluding that the assay-related warning and use of the assay in connection

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[3/] A laboratory developed test is a type of in vitro diagnostic test that is designed, manufactured, and used within a single laboratory. U.S. Food and Drug Administration, Laboratory Developed Tests, *available at*: http://www.fda.gov/MedicalDevices/Productsand MedicalProcedures/InVitroDiagnostics/ucm407296.htm.

with Tysabri treatment were not sufficiently supported by the then-available scientific evidence. FDA did not approve a label change concerning the significance of anti-JCV antibodies until January 2012, *after* Mrs. Amos's PML diagnosis. Thus, as the *Christison* and *Gentile* courts held recently, there is "clear evidence" in the undisputed summary judgment record that FDA would not have permitted warnings about the significance of anti-JCV antibodies at any time before January 2012, when the Agency concluded that the data supported a labeling change. The Plaintiff's JCV-antibody claims are thus preempted by federal law. *Wyeth v. Levine*, 555 U.S. 555, 568, 571-72 (2009).

II. STATEMENT OF UNDISPUTED FACTS

A. *Andrea Amos and Multiple Sclerosis.*

Andrea Amos suffered from MS, a chronic, progressive, and disabling autoimmune disease of the central nervous system ("CNS") (the brain, spinal cord, and optic nerves) (Statement of Undisputed Material Facts ("SF") at ¶) (SF ¶ 16). In MS, inflammatory white blood cells ("WBCs") enter the CNS and attack myelin, a fatty substance that surrounds nerve fibers. (SF ¶ 16). MS causes gradual destruction of the myelin ("demyelination") and resulting nerve damage throughout the brain and spinal cord, leaving scar tissue called "scleroses," which can be seen on magnetic resonance imaging ("MRI") images. (SF ¶ 17). Depending on where in the CNS the demyelination is located, a broad range of symptoms associated with MS can occur, including loss of muscle control, impaired vision, blindness, incontinence, sensory abnormalities, personality changes, cognitive impairment, and disabling fatigue. (SF ¶ 17).[4/] MS is a cause of

[4/] MS has no known cure and there were no disease modifying therapies available to treat the disease until 1993. (SF ¶ 20). While treatment options have been growing, the therapeutic options do not work in all cases. (SF ¶ 20). All of the MS drug treatments have side effects that can impact a patient's ability to use or tolerate the medication. (SF ¶ 20). Tysabri continues to be highly efficacious in treating MS and is an important treatment option prescribed by MS specialists for thousands of patients worldwide. (SF ¶ 22).

major disability, particularly in young people, and most patients will require assistance walking if the progression of the disease process is not arrested. (SF ¶ 18). In severe cases, MS sufferers can be confined to a wheelchair, bedridden, or die from MS complications. (SF ¶ 18).

Dr. David Smith of Rochester, New York diagnosed Andrea Amos with MS in early 2005 when she was 40 years old. (SF ¶ 7). Dr. Smith first saw Mrs. Amos in March 2005, after she had an acute attack of numbness in her legs and feet. (SF ¶ 56). By the time of her MS diagnosis, she had MS attacks for more than 10 years. (SF ¶ 58). In 1992, Mrs. Amos developed symptoms of optic neuritis in her right eye and later in her left eye. (SF ¶ 55).

MRI scans in April 2005 showed that in addition to lesions in her optic nerves, Mrs. Amos had lesions in her spinal cord and in her brain. (SF ¶ 57). In total, lesions affected her entire CNS: her brain, optic nerves, and spinal cord. (SF ¶ 57). In March 2006, Mrs. Amos had a MS relapse. (SF ¶ 60). She exhibited a wobbly gait, and she had weakness and sensory change to her right leg. (SF ¶ 60). She also had numbness in her right leg and the right upper part of her face. (SF ¶ 60). Based on these symptoms, Dr. Smith determined that Mrs. Amos had demyelination in her brainstem. (SF ¶ 60). Dr. Smith testified that these are "… ominous symptoms. She's not going to be walking if you let this go." (SF ¶ 62).

By July 28, 2006, Mrs. Amos had reported two clear MS attacks. (SF ¶¶ 60-61). Dr. Smith's clinical notes reflect Mrs. Amos's concerns: her "principle concern is the heavy burden of cerebral demyelinating disease, and now spinal cord symptoms and the fact that she has had MS attacks since at least July 1993, perhaps earlier with a frequent and sometimes aggressive pattern." (SF ¶ 61).[5/] Mrs. Amos sought aggressive MS treatment, and Dr. Smith's notes state that she "wants aggressive therapy with Tysabri." (SF ¶ 61).

[5/] This clinical visit note further states that "she has never been treated with ABCR drugs," referring to Avonex, Betasaron, Copaxone, and Rebif. (SF ¶ 59).

Because of Mrs. Amos's long MS history and "ominous" symptoms, Dr. Smith recommended aggressive MS treatment using Tysabri. (SF ¶ 62). On July 28, 2006, Dr. Smith prescribed Tysabri to Mrs. Amos and she enrolled in the TOUCH program. (SF ¶ 63, 64). She received her first Tysabri infusion on September 2, 2006. (SF ¶ 68). Over the course of her treatment, she received a total of 62 Tysabri infusions. (SF ¶ 69).

Throughout more than four years of Tysabri treatment under Dr. Smith's care, Mrs. Amos tolerated Tysabri well, her MS symptoms were stable, and periodic MRIs of her head and spine showed no MS progression. (SF ¶ 70). Dr. Smith thus continued Mrs. Amos's Tysabri treatment until May 4, 2011 when Mrs. Amos received her last Tysabri infusion in Dr. Smith's practice. (SF ¶ 70).

In May 2011, Mrs. Amos began seeing a different neurologist, Louis Medved, M.D. (SF ¶ 73). At that time, Mrs. Amos reported to Dr. Medved the onset of double vision (diplopia) over the prior month. (SF ¶ 73). Following an MRI, Mrs. Amos returned to Dr. Medved's office on June 1, 2011. In deciding whether to prescribe Tysabri to Mrs. Amos, Dr. Medved considered that Mrs. Amos had been on Tysabri for over two years but had never taken immunosuppressant medication. (SF ¶ 119). Dr. Medved's clinical note also explained that he understood that the presence of anti-JCV antibodies suggested a higher PML risk and that he had been informed that Mrs. Amos tested positive for JCV antibodies while participating in a clinical trial. (SF ¶ 121, 122). He accounted for all three of these risk factors, as reflected in his clinical note. (SF ¶ 123, 124).[6/]

Dr. Medved, through his physician's assistant Brandon Yehl, wrote a new Tysabri prescription for Mrs. Amos on June 1, 2011. (SF ¶ 76). Mrs. Amos received two infusions in Dr.

6/ He calculated her PML risk as 1/500 given that she had two risk factors: duration of treatment greater than two years and the presence of anti-JCV antibodies. (SF ¶ 124).

Medved's office, on June 3, 2011 and June 29, 2011. (SF ¶ 77). She was diagnosed with PML in mid-July 2011. (SF ¶ 78). She died on September 20, 2011. (SF ¶ 78).

B. *Tysabri (Natalizumab).*

Tysabri is a recombinant, humanized, monoclonal antibody that inhibits the trafficking of inflammatory WBCs into the CNS, and thereby protects the myelin from attack and resulting nerve cell damage. (SF ¶ 21). Because of this mechanism of action, Tysabri is highly effective at interrupting the MS disease process, decreasing the number of MS relapses, and substantially reducing and delaying nerve damage and resulting disability. (SF ¶ 22). FDA approved Tysabri in November 2004 for treatment of relapsing forms of MS based on clinical trial data demonstrating Tysabri's high efficacy in interrupting the MS disease process and reducing disability, combined with a strong safety profile. (SF ¶ 23).

C. *PML is a Known Risk of Tysabri.*

A few months after the drug went on the market, in February 2005, Defendants received reports that two MS patients who were participating in ongoing clinical trials of Tysabri used in combination with Avonex (another MS medication) had developed PML. (SF ¶ 25). PML had never before been associated with Tysabri, Avonex, or MS. In the absence of a compromised or suppressed immune system PML was an extraordinarily rare viral brain infection caused by a ubiquitous and usually harmless virus called JCV. (SF ¶¶ 26-29).[7/] In response to the reports of the two PML cases in the Tysabri/Avonex-treated MS population, Defendants voluntarily

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[7/] JCV is an acronym for "John Cunningham virus" and is named after the patient who was the subject of a case report in which JCV was first described. It is a common and ubiquitous virus that infects the majority of adults. *See Christison*, 2016 U.S. Dist. LEXIS 110273, at *11, ¶ 8. It is generally harmless except in cases of severe immunosuppression resulting from AIDS, immunosuppressive drugs used in treating cancer and in preventing post-transplant tissue rejection, and certain biologic medications that target the immune system.

withdrew Tysabri from the market and suspended its use in clinical trials so that the PML risk could be evaluated and quantified. (SF ¶ 30).[8/]

After months of reviewing the safety data, Biogen sought FDA approval to reintroduce the drug to the market with new labeling concerning the PML risk. (SF ¶ 32). On March 2, 2006, Biogen submitted extensive data to FDA including, among other things, the results of antibody testing of blood serum samples from Tysabri clinical trial patients using an anti-JCV antibody assay developed by the National Institutes of Health ("NIH"). (SF ¶ 35). The report concluded that the data were insufficient and there was no consensus on a clinically relevant cutoff for a "positive" assay result at that time. (SF ¶ 35).

FDA convened an Advisory Committee of experts to both evaluate the benefit/risk profile of Tysabri in light of the severity of MS and the available treatments and to make a recommendation to FDA as to whether the drug should be available for use in the treatment of MS. After a review of the data and a public hearing at which the experts heard testimony from MS specialists, patient advocacy groups, and MS patients in support of Tysabri's return to the market, the Advisory Committee recommended that FDA approve Tysabri's return to the market with new labeling and certain restrictions on its use. (SF ¶¶ 37-38). On June 5, 2006, FDA accepted the Advisory Committee's recommendations and approved Tysabri's return to the market as a monotherapy (*i.e.*, a drug that is taken alone) for relapsing forms of MS, subject to a

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8/ In the subsequent safety review, a third PML case was identified in a patient in Belgium who was participating in a clinical trial of Tysabri in the treatment of Crohn's disease. It was determined that the clinical trial investigator had misdiagnosed the patient's PML as a brain tumor. (SF ¶ 33).

number of significant new requirements to mitigate the PML risk, including a black box warning and the TOUCH prescribing program. (SF ¶ 38).[9/]

D. *FDA Required a Black Box PML Warning and the TOUCH Prescribing Program.*

First, FDA mandated that the labeling include a "black box" or "boxed" warning informing prescribers that Tysabri use carries with it the risk of developing PML. (SF ¶ 40-41). A "boxed" warning is the strongest warning required or permitted by FDA in prescription drug labeling and highlights particularly important information that physicians must take into account when considering whether to prescribe a drug to a particular patient.[10/] (SF ¶¶ 9, 38). At the time Mrs. Amos was first prescribed Tysabri in July 2006, the black box warning read as follows (emphasis in original):

> WARNING
>
> TYSABRI® increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Although the cases of PML were limited to patients with recent or concomitant exposure to immunomodulators or immunosuppressants, there were too few cases to rule out the possibility that PML may occur with TYSABRI® monotherapy.
>
> - Because of the risk of PML, TYSABRI® is available only through a special restricted distribution program called the TOUCH™ Prescribing Program. Under the TOUCH™ Prescribing Program, only prescribers, infusion centers, and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute, or infuse the product. In addition, TYSABRI® must be administered only to patients who are enrolled in and meet all the conditions of the TOUCH™ Prescribing Program **(see WARNINGS, Progressive Multifocal Leukoencephalopathy; and WARNINGS, Prescribing, Distribution, and Administration Program for TYSABRI®)**.

9/ FDA's approval letter advised that FDA had reviewed Defendants' submissions through June 2, 2006, which includes the March 2006 submission discussing NIH's assay.

10/ *See* 21 C.F.R. § 201.57(c)(1); 44 Fed. Reg. 37434, 37448 (FDA June 26, 1979) ("[T]o ensure the significance of boxed warnings in drug labeling, they are permitted in labeling only when specifically required by FDA."); *Kaleta v. Abbott Labs Inc.*, 87 F. Supp. 3d 916, 924 (S.D. Ill. 2015).

- Healthcare professionals should monitor patients on TYSABRI® for any new sign or symptom that may be suggestive of PML. TYSABRI® dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended **(see CONTRAINDICATIONS and WARNINGS, Progressive Multifocal Leukoencephalopathy).**

(SF ¶ 12). The Tysabri prescribing information also included a "Warnings" section that contained two pages of warnings, in bold print, about the PML risk, including the fact that the absolute PML risk as well as an individual patient's risk factors "cannot be precisely estimated." The "Warnings" section began:

> "**Progressive multifocal leukoencephalopathy, an opportunistic infection caused by the JC virus that typically occurs in patients that are immunocompromised, has occurred in 3 patients who received TYSABRI® in clinical trials (see BOXED WARNING). . . There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs. It is not known whether early detection of PML and discontinuation of TYSABRI® will mitigate the disease.**"

(SF ¶ 42). The labeling also contained an "Indications and Usage" section stating that "Because TYSABRI® increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability (**see BOXED WARNING AND WARNINGS, Progressive Multifocal Leukoencephalopathy)**, TYSABRI® is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate multiple sclerosis therapies." (SF ¶ 43). This language has remained in the black box warning since the 2006 reintroduction of Tysabri to the market.

Defendants also included PML warnings in Tysabri's Medication Guide, provided by prescribers to patients, which stated: "PML usually happens in people with weakened immune systems. No one can predict who will get PML. There is no known treatment, prevention, or cure for PML." (SF ¶ 45). A version of the boxed warning, and the numerous other PML warnings, were included in the drug's labeling before and throughout the nearly five-year period during

which Mrs. Amos received monthly Tysabri infusions.

Second, FDA determined that because of the significance of the PML risk, as a condition of the drug's return to the market, Tysabri would be a "restricted" drug that could only be prescribed, dispensed, or used by treating neurologists, specialty pharmacies and patients who are enrolled in a detailed Risk Evaluation and Mitigation Strategy Program ("REMS" program). (SF ¶ 46). The Tysabri REMS program is called the "TOUCH" program.[11/] In its June 5, 2006 re-approval letter, FDA expressly prohibited Biogen from altering the REMS program's content without prior FDA approval. (SF ¶ 54).

The TOUCH Program was intended to "assess the risk of [PML] associated with [Tysabri], minimize the risk of PML, minimize death and disability due to PML, and promote informed risk-benefit decisions regarding TYSABRI use." (SF ¶ 49). TOUCH is also designed to ensure that treating neurologists (specialists whose field includes the diagnosis and treatment of both MS and PML) understand the PML risk associated with Tysabri treatment and inform patients of that risk. (SF ¶ 50). Participating neurologists must acknowledge, in writing, that they are aware of and understand the PML risk. Before prescribing Tysabri and enrolling the patient in the TOUCH program, the physician must also obtain a written acknowledgement from each patient that the patient understands the PML risk.[12/] (SF ¶ 50). The TOUCH enrollment form warns about the PML risk, and by signing the patient acknowledges that "[m]y chance of getting PML may be higher if I am treated with other medicines that can weaken my immune system, including other MS treatments," and, initially, that "[i]t is also not known if treatment for a long

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11/ TOUCH is an acronym for Tysabri Outreach: Unified Commitment to Health.

12/ The Tysabri physician package insert also included the requirements of the TOUCH program and the prescribing physician's responsibilities under that program. (SF ¶ 44).

period of time with TYSABRI can increase my chance for PML." (SF ¶ 13). Mrs. Amos and her physicians enrolled in TOUCH and signed the required forms. (SF ¶¶ 64, 66).

Following enrollment in TOUCH and the initiation of Tysabri treatment, at every monthly Tysabri infusion thereafter, specially trained infusion nurses enrolled in the TOUCH program must obtain the patient's acknowledgement and confirmation that the patient has read the Medication Guide, which includes the warnings concerning the PML risk associated with Tysabri that are set forth in the drug's labeling. (SF ¶¶ 44, 51). The infusion nurse must ask the patient a series of questions about the patient's knowledge of the PML risk and inquire about the emergence of any new symptoms that suggest a change in neurological condition that could possibly be an early sign of PML. (SF ¶ 42). If any such changes are reported, the Tysabri infusion cannot be given without further evaluation and approval by the prescribing neurologist. (SF ¶ 53).

E. *Defendants' Pharmacovigilance Efforts Led to the Discovery of Three PML Risk Factors That Resulted in Amendments to Tysabri's PML Warnings.*

After the initial PML cases were reported in February 2005, Defendants embarked on a broad-based research program and in regular communication with FDA maintained an intensive pharmacovigilance protocol to study and better understand PML. The focus of these efforts was to determine whether there was any way to "stratify" the PML risk (*i.e.*, to identify individual risk factors for PML that a physician could use in making prescribing decisions and in counseling patients). (SF ¶ 30). Specifically, Defendants sought to determine why a small number of Tysabri patients get PML when the majority of Tysabri patients are infected with JCV, but do not get PML.

Between 2008 and 2012, as a result of growing use and experience with Tysabri and Tysabri-associated PML, three individual risk factors were identified and quantified: (1) duration

of Tysabri treatment; (2) prior treatment with immunosuppressant drugs; and (3) the detection of anti-JCV antibodies in blood, using an FDA-cleared assay that Biogen scientists developed and analytically and clinically validated for use with Tysabri.[13/] (SF ¶¶ 82-98).

1. In November 2009, While Mrs. Amos was Prescribed Tysabri, FDA Approved a Label Update to Include the Duration of Treatment as a PML Risk Factor.

At the time Tysabri was returned to the market in June 2006, Defendants and FDA considered whether the PML risk might be associated with duration of Tysabri treatment—with the risk increasing with longer treatment duration—but there were insufficient data to support any conclusion.[14/] (SF ¶ 80). This uncertainty was stated expressly in the Tysabri label. (SF ¶ 42). After the two cases of PML in MS patients reported in the clinical trials before Tysabri's return to the market (and a third case in a Crohn's disease patient (SF ¶¶ 33, 42)), there were no additional confirmed cases of Tysabri-associated PML for Defendants to analyze until July 2008.

At that time, the first two Tysabri-associated cases occurring after Tysabri's re-introduction to the market were confirmed. (SF ¶ 80). At Biogen's request, in August 2008, FDA approved an update to the Tysabri labeling to explain that: "There is limited experience beyond two years of treatment. The relationship between the risk of PML and the duration of treatment is unknown, but most cases of PML were in patients who received more than one year of treatment." (SF ¶ 83).

13/ "Analytically validated" refers to an anti-JCV antibody assay that has been shown to accurately detect anti-JCV antibodies to prove prior exposure to the JC virus. (SF ¶ 101). "Clinically validated" refers to an anti-JCV antibody assay that has been shown through clinical trial data to be useful to physicians in the clinical setting by providing information regarding the association of anti-JCV antibodies to an individual's PML risk. Clinical validation is an FDA requirement for any labeling claim or the marketing of any drug or device for use in the diagnosis or treatment of a disease. (SF ¶ 102).

14/ Two of the three PML cases occurred after a median of 120 weeks of treatment, while the third occurred after 32 weeks of treatment. (SF ¶¶ 42, 81).

Over time, confirmed PML cases reported to Biogen increased in number and in frequency. In September 2009, Biogen and FDA both independently concluded, based on analyses of the post-marketing PML cases, that longer duration of Tysabri treatment increases the PML risk. Based on that data, and at Biogen's request, FDA approved an update to the Tysabri label in November 2009 to read: "In patients treated with TYSABRI, the risk of developing PML increases with longer treatment duration, and for patients treated for 24 to 36 months is generally similar to the rates seen in clinical trials. There is limited experience beyond 3 years of treatment." (SF ¶ 86).

This updated language was in the Tysabri label from that point on and throughout the remaining time that Dr. Smith prescribed the drug to Mrs. Amos until May 2011. (SF ¶ 86). The duration risk factor was also in the label when Dr. Medved prescribed Tysabri to Mrs. Amos in June 2011. (SF ¶ 42).

2. In July 2010, While Mrs. Amos was Prescribed Tysabri, FDA Approved a Label Update to Include Prior Treatment with an Immunosuppressant Drug as a PML Risk Factor.

Defendants continued to analyze all PML cases for possible individual risk factors, and in July 2010 FDA approved Biogen's proposed update to the Tysabri label to reflect Biogen's conclusion that prior treatments with immunosuppressant drugs is an independent PML risk factor. (SF ¶ 87). The supplemented labeling stated: "The risk of PML is also increased in patients who have been treated with an immunosuppressant prior to receiving Tysabri. This increased risk appears to be independent of Tysabri treatment duration." (SF ¶ 87). This language was in the label from that point on and throughout Dr. Smith's treatment of Mr. Amos's MS with monthly Tysabri infusions. This risk factor was also in the label when Dr. Medved prescribed Tysabri to Mrs. Amos. (SF ¶123).

3. Biogen Researched and Developed an Assay to Test for the Presence of Anti-JCV Antibodies and Concluded that a Positive Assay Result is a Marker of Increased PML Risk.

It is basic medical knowledge that PML is caused by the JC virus and this fact was stated in the Tysabri label when FDA approved its return to the market in 2006. (SF ¶ 27). It is also common scientific knowledge that the presence of anti-JCV antibodies is biologic evidence that a person has been exposed to JCV. (SF ¶¶ 28-29). FDA was aware of this information when it evaluated Tysabri before its return to the market in 2006. In fact, in evaluating Tysabri before its return to the market in 2006, FDA requested that Biogen conduct an assessment of the presence of JCV antibody at baseline for patients entering clinical trials. (SF ¶ 34). On March 2, 2006, Biogen submitted to FDA a report on the results of antibody testing of serum samples conducted at the NIH, which was inconclusive. (SF ¶ 35). After this submission, FDA approved Tysabri's return to the market on June 5, 2006, but FDA did not require JCV antibody testing or any reference to JCV antibody status in the label. (SF ¶¶ 38-39).

When FDA re-approved Tysabri's return to the market in 2006, there were no statistically significant data from which it could be determined whether the presence of circulating anti-JCV antibodies indicated that someone is at a higher or lower risk of getting PML. (SF ¶ 95). Although a positive finding on a JCV antibody assay would indicate a necessary prerequisite to JCV infection, without sufficient data, a positive finding could not be used as evidence of a relatively higher PML risk and a negative finding could not be used as evidence of relatively lower PML risk. (SF ¶ 96).[15/]

15/ From the time Tysabri was removed from the market in 2005 through 2010, Defendants' scientists and others in the field also pursued what they thought to be the most likely risk stratification tool by devoting research efforts to finding JC virus DNA in the blood through Polymerase Chain Reaction ("PCR") assay testing. (SF ¶ 89). PCR testing was thought to be the most likely risk stratification tool because to develop PML a person must be infected with the JC virus and the virus must move through the body to the CNS. The virus must mutate into a form

By late 2009, Biogen scientists had developed an analytically validated antibody assay that could reliably detect circulating anti-JCV antibodies in the blood with acceptably low false-positive and false negative rates. (SF ¶ 100). Using this assay, Biogen scientists developed data from a small number of PML cases for which pre-PML blood serum samples were available for testing that suggested the presence of circulating antibodies might be a predictive indicator or "marker" of higher relative PML risk. (SF ¶ 100). Specifically, Biogen discovered that 100% (11 of 11) of PML patients for whom pre-PML blood samples were available for testing had detectable anti-JCV antibodies, using an assay that would predict (based on population studies of the prevalence of JCV antibodies using the assay) a rate of exposure to JCV among the MS population of 54%. (SF ¶ 104).

Biogen therefore convened Advisory Boards of MS experts and regulatory experts to evaluate these findings. (SF ¶ 105). At an Advisory Board meeting on December 9, 2009, the experts opined that the "data on the assay was too preliminary to be of predictive value" regarding PML. (SF ¶ 105). In an Advisory Board meeting on December 12, 2009, most (but not all) of the medical experts agreed that based on the limited data available, the idea of using anti-JCV antibody testing in risk stratification had potential and that Biogen should pursue further research in this area. (SF ¶ 105).

Defendants' scientists continued to search for pre-PML serum samples (blood samples drawn and stored before the patient was diagnosed with PML and that remained available for testing) from physicians around the world to collect more data regarding anti-JCV antibodies in PML patients and the prevalence of antibodies in the MS patient population ("seroprevalence")

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that can replicate in CNS tissue. (SF ¶ 89). By 2010, PCR testing was found "unlikely to be useful" as a PML risk stratification tool in data published in the Annals of Neurology. (SF ¶ 90). *Christison*, 2016 U.S. Dist. LEXIS 110273, at *46.

generally. They also continued to work on improving the sensitivity and specificity of the anti-JCV antibody assay, *i.e.*, minimizing false negatives and false positives. Ultimately Biogen had data from testing 17 pre-PML blood samples that supported the hypothesis that circulating anti-JCV antibodies could be a predictive biomarker of increased PML risk in Tysabri-treated MS patients. (SF ¶ 109). Biogen published these results in September 2010. (SF ¶ 109).

4. In September 2010, FDA Rejected Biogen's Proposal to Change Tysabri's Label to Reference Anti-JCV Antibody Testing.

Based on this data, on September 8, 2010, representatives of Biogen and Elan met with regulators at FDA's CDER to discuss a potential labeling change based on Defendants' ongoing research regarding the significance of anti-JCV antibodies. (SF ¶ 107). Specifically, Biogen proposed to amend the label to recommend that patients be screened for the antibodies using the Biogen-developed assay and that the results of that screening be used as one factor in the neurologists' benefit/risk evaluation of Tysabri treatment in individual patients. (SF ¶ 108). FDA rejected the proposal. As detailed in FDA's official meeting minutes, FDA concluded that the then-available scientific data were insufficient to support inclusion of a warning about the significance of anti-JCV antibody status in Tysabri's labeling:

> **Sponsor Question 5:** Does the Agency agree that the proposed labeling concepts reflect the information that should be provided in the prescribing information for TYSABRI?
>
> **The proposed labeling concepts are as follows:**
>
> - Individual anti-JCV antibody status is one consideration in determining the benefit/risk of TYSABRI
> - Screening for serum anti-JCV antibody should be performed prior to initiating therapy and annually thereafter
> - Patients who are anti-JCV negative have a lower risk of developing PML than those who are anti-JCV antibody positive
> - There is an increased risk for PML in anti-JCV antibody positive patients
>
> **FDA Pre-Meeting Comments:** As discussed in the answers above, ***the Division does not believe that there is currently sufficient information to support the***

> ***clinical utility of the anti-JCV antibody assay in determining the risk for PML*** and the benefit/risk of TYSABRI. The Division does, however, agree that the test may be promising and that it should [be] studied carefully to address the concerns identified in our responses.

(SF ¶ 108) (emphasis added).

FDA concluded that the data did not support a labeling change concerning anti-JCV antibody testing because there was an insufficient number of PML cases for which Biogen had pre-PML blood samples available for testing. (SF ¶ 109). FDA stated that it was "too early" in the analysis of this methodology "to determine the value of this marker as a PML risk stratification tool." (SF ¶ 109). FDA was also concerned that the samples Biogen used in its testing were selected retrospectively, rather than being drawn prospectively. (SF ¶ 109). FDA's official meeting minutes reflect these and numerous other concerns regarding the data available as of September 2010 did not support Biogen's proposed labeling change:

- "The results are based on only a small population (only 17 patients had pre-PML antibody status tested)";
- "It appears that the results you describe are based on testing that was done after patients had already been exposed to Tysabri. It would be more useful, in determining the value of the test, if there were results of serial anti-JCV antibody tests for patients beginning before exposure to Tysabri and then at fixed times following administration of Tysabri (e.g. to identify whether rising antibody titers are predictive of PML)";
- "It is not clear how these results would guide therapy in antibody positive patients";
- "Based on this we are concerned about the stability of the determination, and the utility in using it to predict development of PML";
- "We do not agree that the proposed data package is sufficient to demonstrate the clinical utility of the anti-JCV antibody assay.
- "Based on the information you have presented, antibody-negative patients would have a lower risk of developing PML. It is not clear how this information would help guide therapy, particularly given the uncertainty related to the stability of the result in a given individual over time."[16/]

16/ A patient may test "negative" for the presence of antibodies to the JC virus and then test "positive" on a subsequent test and vice versa. This could be the result of subsequent first

(SF ¶ 109).

5. In November 2010, FDA Also Rejected Biogen's Proposal to Make the Anti-JCV Antibody Assay Available to Tysabri Prescribers.

On November 18, 2010, Defendants again met with FDA regulators, this time at FDA's CDRH, the FDA division responsible for clearing diagnostic tests and medical devices. They discussed Biogen's proposal to make Biogen's anti-JCV antibody assay available to Tysabri prescribers as an LDT kit before FDA clearance of the Biogen assay and related Tysabri labeling changes. (SF ¶ 110). FDA again rejected Biogen's proposal and reiterated in the official meeting minutes FDA's conclusion that "[t]he usefulness of this test in treatment with Tysabri has not been established." (SF ¶ 111). FDA further stated that the assay could not be made available for use with Tysabri until both (1) the antibody assay was cleared by FDA for use in the clinical setting as a medical device, and (2) a labeling change for Tysabri was approved after the submission of clinical data demonstrating the "clinical utility" of an assay finding (positive or negative) to the physician's evaluation of an individual patient's PML risk. (SF ¶ 112).

FDA's official meeting minutes document FDA's multiple concerns regarding the sufficiency and significance of the assay data and its usefulness to physicians in prescribing Tysabri, stating among other comments:

- "This specific assay does not have any intended use other than to be used with the drug. Therefore, an LDT could not be cleared/approved before the assay is mentioned in the drug label";
- "The Agency confirmed that an LDT clearance for the proposed indications could only take place after the clinical division had approved the label change that described the clinical utility of the assay";
- "If the drug labeling specifies this device as critical in order to determine therapy, the sponsor/test must comply with FDA regulations for in vitro diagnostic devices";

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exposure, while on the drug, to the common and ubiquitous virus, or the result of a false negative or false positive test. This phenomenon is referred to as "seroconversion." The current label states that the rate of seroconversion is between 3% and 8%. (SF ¶ 97).

- "The information provided does not allow us to determine the clinical utility for the intended use claims";
- "[t]he anti-JCV antibody assay has limited positive predictive value . . ."; and
- "Your proposal to assess the agreement between your commercial kit and your LDT test (which is essentially the same device) is not acceptable as a means to evaluate your device performance. As stated above, we recommend that you assess the clinical performance of your device in the context of the drug trial."

(SF ¶ 112) (emphasis added).

In light of FDA's rejection of Biogen's proposals to change the label and to make the assay available to neurologists as an LDT, Biogen continued its search for pre-PML samples in patients diagnosed with Tysabri-associated PML. Biogen continued with its sponsorship of two prospective clinical trials of the anti-JCV antibody assay, STRATIFY I and STRATIFY II, which it commenced in March 2010. (SF ¶ 113).[17/]

6. After the Two Clinical Trials and the Submission of Additional Data, FDA Approved an Amendment to Tysabri's Label Concerning the Significance of Anti-JCV Antibodies in January 2012.

In October 2011, after Mrs. Amos's PML diagnosis, Biogen presented to FDA additional data that it had developed in connection with its ongoing research and evaluation of PML cases for which pre-PML serum samples were available for testing, and data developed in the two clinical trials. (SF ¶ 116). Biogen again requested that the Tysabri label be supplemented to include information concerning the significance of detectable anti-JCV antibodies using the Biogen-developed assay. (SF ¶ 115). On January 20, 2012, FDA publicly announced that it had cleared Biogen's STRATIFY JCV Antibody Assay for use with Tysabri treatment and approved an associated Tysabri labeling change to reflect this information. (SF ¶ 117).

17/ While Dr. Smith prescribed Tysabri to Mrs. Amos, he enrolled her in the STRATIFY II clinical trial to determine whether, using the Biogen-developed assay, she had anti-JCV antibodies. (SF ¶ 121). On or about August 6, 2010, a laboratory reported that anti-JCV antibodies were "detected" in Mrs. Amos's blood sample. (SF ¶ 121).

F. *Plaintiff's Complaint.*

On July 19, 2013, Plaintiff commenced this action against Biogen and Elan. The Court dismissed Plaintiff's claims for design defect, alleged violations of New York's General Business Law, and fraud. The crux of the remaining claims for negligence (Count I), strict products liability (Count II), failure to warn (Count IV), negligent misrepresentation (Count V), breach of implied warranty (Count VI), and wrongful death (Count IX) is that there were three alleged deficiencies in the FDA-approved black box warning and related labeling concerning the PML risk while Mrs. Amos received Tysabri infusions between 2006 and 2011. These alleged deficiencies mirror the changes that were made to the Tysabri label after the drug was re-launched in 2006. Specifically, Plaintiff alleges that Defendants failed adequately to warn about the increased risk of PML associated with (1) duration of Tysabri treatment, (2) prior immunosuppressant treatment, and (3) the significance of anti-JCV antibody assay results. Compl. ¶¶ 69, 70, 71, 123, 125, 130, 138. Plaintiff cannot prevail on any of these warnings claims and summary judgment must enter in Defendants' favor under Rule 56 as a matter of law.

III. ARGUMENT

A. *Choice of Law*

The Parties do not dispute, and the Court found, that the substantive law of New York governs the issues in this case. *See* Decision and Order on Motion to Dismiss, *Amos v. Biogen Idec Inc.*, Dkt. No. 29, at 6-17 (June 25, 2014).

B. *Summary Judgment Standard*

Federal courts must grant summary judgment when "there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law" (Fed. R. Civ. P. 56(a)) or when a plaintiff "fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial."

Celotex Corp. v. Catrett, 477 U.S. 317, 322 (1986). Summary judgment is appropriate where, drawing all reasonable inferences in favor of the non-moving party, "there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a); *see also Celotex Corp.*, 477 U.S. at 322-23. An issue is genuine only if there is a sufficient evidentiary basis on which a reasonable jury could find for the non-movant. *See Anderson v. Liberty Lobby, Inc*., 477 U.S. 242, 248 (1986)). Once the moving party demonstrates the absence of a triable issue, the nonmoving party must come forward with specific facts showing that there is a genuine issue of material fact for trial, and conclusory allegations, conjecture, and speculation are insufficient to create a genuine issue of fact. *Shannon v. New York City Transit Auth.*, 332 F.3d 95, 99 (2d Cir. 2003). Summary judgment is available if the party with the burden of proof at trial fails to present in the summary judgment record, taking everything it says as true and drawing all reasonable inferences in its favor, sufficient facts to warrant a finding in its favor. *Anderson*, 477 U.S. at 248.

C. *Defendants are Entitled to Summary Judgment Because—as Two Courts Have Decided—Tysabri's Warnings Concerning the Risk of PML with Tysabri Treatment Were Adequate as a Matter of Law.*

The undisputed summary judgment record establishes that Plaintiff cannot prevail on a failure to warn claim because Tysabri's extensive PML warnings, including the black box warning, reinforced by the TOUCH Program requirements, were as a matter of law adequate to inform Drs. Smith and Medved of the PML risk.[18/] The PML warnings warned of the "precise

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[18/] A legally adequate warning "need not be perfect, only 'reasonable.'" David G. Owen, *Products Liability Law* § 9.2, at 593 (2d ed. 2008); *see In re Rezulin Prods. Liab. Litig.*, 331 F. Supp. 2d 196, 202 (S.D.N.Y. 2004) (the "crux of the inquiry is whether the warning is reasonable under the circumstances"); *see also, Meridia Products Liab. Litig. v. Abbott Labs.*, 447 F.3d 861, 867 (6th Cir. 2006) (affirming summary judgment because of the label's warning about the plaintiff's injury was "reasonable under the circumstances"); *Nolan v. Dillon*, 261 Md. 516, 523 (1971) ("The duty is to give a reasonable warning, not the best possible one."); *see also, e.g., Ralston v. Smith & Nephew Richards, Inc.*, 275 F.3d 965, 975 (10th Cir. 2001); *Felix v.*

malady" incurred by Mrs. Amos. Where the warnings are clear, the Court may resolve the duty to warn issue as a matter of law. *See, e.g., McDowell v. Eli Lilly & Co.*, 58 F. Supp. 3d 391, 403 (S.D.N.Y. 2014) ("The adequacy of the warning provided to a prescriber may be determined as a matter of law."); *Martin v. Hacker*, 83 N.Y.2d 1, 10 (1993); *Calisi v. Abbott Labs., No.* No. 11-10671-DJC, 2013 US Dist. LEXIS 139257 at *59-60 (D. Mass. Sept. 27, 2013).

New York has adopted the principle that prescription drugs are "unavoidably unsafe" products as set forth in comment k[19/] to Restatement (Second) of Torts, § 402A. *See, e.g., Martin*, 83 N.Y.2d at 8; *Wolfgruber v. Upjohn Co.*, 423 N.Y.S.2d 95, 96-97 (N.Y. App. Div. 1979). As a result of comment k, a prescription drug is not deemed "defective" simply because it has harmful side effects. A pharmaceutical manufacturer's duty is to act reasonably in the manufacture of its drug products and to adequately warn physicians of the risks inherent in the use of those products based on the information reasonably known at that time. *See, e.g., McDowell*, 58 F. Supp. 3d at 402, 401-02; *Martin*, 83 N.Y.2d at 8 (duty to warn prescribers of "potential dangers in its prescription drugs that it knew, or, in the exercise of reasonable care, should have known to exist"). The physician is an "informed intermediary." *See Martin*, 83

Hoffman-LaRoche, 540 So. 2d 102, 105 (Fla. 1989) (awarding summary judgment to the defendant where "reasonable persons" could not disagree that label warned of the specific risk); *Shanks v. A.F.E. Indus., Inc.*, 275 Ind. 241, 249 (1981); *Pfizer, Inc. v. Jones*, 221 Va. 681, 684 (1980) (agreeing with *Nolan v. Dillon* and setting aside a jury award because the defendant only needed to give a reasonable warning, not the "best possible one").

[19/] Comment k provides, in pertinent part: "There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs. . . . Such a product, properly prepared, and accompanied by proper directions and warning, ***is not defective, nor is it unreasonably dangerous***. . . . The seller of such products, again with the qualification that they are properly prepared and marketed, and proper warning is given, where the situation calls for it, is not to be held to strict liability for unfortunate consequences attending their use, merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk." Restatement (Second) of Torts § 402A, comment k (1965) (emphasis added).

N.Y.2d at 9.

A warning is adequate as a matter of law "if it provides specific detailed information on the risks of the drug." *Martin*, 83 N.Y. 2d at 10. As stated by a New York federal court, "[i]t has long been the law in New York that prescription medicine warnings are adequate, when, as here, information regarding the 'precise malady incurred' was communicated in the prescribing information." *Alston v. Caraco Pharm., Inc.*, 670 F. Supp. 2d 279, 284 (S.D.N.Y. 2009) (quoting *Wolfgruber*, 423 N.Y.S.2d at 96-97); *see also Gaynor v. Merck Sharp & Dohme Corp.*, No. 12-1492, 2014 U.S. Dist. LEXIS 82003, at *33 (D.N.J. June 17, 2014) (applying New York law) (holding that "[i]n such instances, when a plaintiff claims to be injured in a manner that is addressed by warnings provided to his physician, summary judgment is granted on failure to warn claims").

To determine the adequacy of the PML warnings, the Court should apply the framework set out in *Martin* (the "*Martin* test"). Specifically, the Court should consider the seriousness of the risk, and then determine "whether the warning is accurate, clear, consistent on its face, and whether it portrays with sufficient intensity the risk involved in taking the drug." *McDowell*, 58 F. Supp. 3d at 403 (citation omitted); *see also Martin*, 83 N.Y.2d at 10. A warning is "clear" if it is "direct, unequivocal and sufficiently forceful to convey the risk." *Id*. (*quoting Martin*, 83 N.Y.2d at 11). Finally, the warning should be "evaluated as a whole and not through the nitpicking prism of an interested legal advocate after the fact." *Id*. The Court must consider "if, when read as a whole, the warning conveys a meaning as to the consequences that is unmistakable." *Martin*, 83 N.Y.2d at 12.

Here, Plaintiff's claim that the Tysabri label did not adequately warn of the risk of PML fails under the *Martin* test. The Tysabri labeling specifically alerts physicians to the potential risk

of PML. It does so in a black box warning that appears in the very first page, paragraph, and sentence of the label: "TYSABRI® increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability." (SF ¶ 12). Throughout Mrs. Amos's Tysabri treatment, the Tysabri warnings fully disclosed the risk of the precise harm suffered by Mrs. Amos (PML), the cause of the harm (JCV), the treatment options should the patient get PML (none), and the likely potential outcome or consequences of getting PML (death or severe disability). Moreover, once Defendants established sufficient data showing the duration and then the prior immunosuppressant use risk factors, they went to FDA and FDA approved the addition of these risk factors to the Tysabri label. (SF ¶86, 87).[20/] Plaintiff cannot point to any evidence in the summary judgment record that could demonstrate that Defendants had earlier knowledge of statistically significant data before the PML risk factors were added to Tysabri's label.

In addition to the boxed warning, Plaintiff's neurologists were informed extensively about the PML risk through the TOUCH program. They could only prescribe the drug after enrolling in the TOUCH program, acknowledging in writing that they understood the PML risks, enrolling their patients in the TOUCH program, and completing the TOUCH program forms and requirements. These unusual and robust prescribing requirements strongly reinforce the severity of the PML risk described in detail in the label.

20/ Plaintiff cannot rely on evidence of the Tysabri labeling changes to prove an alleged failure to warn. Fed. R. Evid. 407. Rule 407 precludes the use of "subsequent remedial measures" to impose liability. A state appellate court recently vacated a final judgment and remanded the case for a new trial where the trial court permitted evidence that the Accutane label was changed after plaintiff stopped taking the drug. *Rossitto v. Hoffman La-Roche Inc.*, No. A-1236-13T1, 2016 N.J. Super. Unpub. LEXIS 1714, at *46-47 (N.J. Super. Ct. App. Div. July 22, 2016).

To put it in terms of the *Martin* test, the black box PML warning and Tysabri labeling concerning the PML risk as a whole "conveys a meaning as to the consequences that is unmistakable" and could not possibly have been more clear, consistent, or stronger (there is no such thing as a "black box plus" warning)[21/] to warn physicians prescribing Tysabri of the PML risk and the severity of that risk. *See Martin*, 83 N.Y. 2d at 12; *McDowell*, 58 F. Supp. 3d at 403; *In re Accutane*, No. 271 (MCL), 2015 N.J. Super. Unpub. LEXIS 1216, at *36-37 (N.J. Super Ct. Apr. 2, 2015) ("Taken as a whole, the warning system crafted by Defendants conveys a meaning as to potential risks and consequences that is unmistakable …. At multiple points, IBD is explicitly communicated to the prescribing physician as a potential risk of Accutane ingestion.").

On the identical FDA regulatory record, the *Gentile* and *Christison* courts both held that Tysabri's PML warnings were adequate as a matter of law. Applying New York law, the *Gentile* court held that the black box warning "explicitly warned against the precise risk (developing PML) that [plaintiff] ultimately suffered, and fully disclosed the serious consequences of that disease." 2016 Mass. Super. LEXIS 238, at *16. "[W]hen a plaintiff claims to be injured in a manner that is addressed by warnings provided to his physician, summary judgment is granted on failure to warn claims." *Id.* at *15 (citing *Alston*, 670 F. Supp. 2d at 284). Similarly, the *Christison* court reasoned: "[t]hroughout the label, the risk of PML is highlighted . . . [T]he black box warning explains that Tysabri increases the risk of PML, which 'usually leads to death or severe disability.' The label does not qualify or minimize the risk of PML and explains the limitations under which Tysabri may be taken." 2016 U.S. Dist. LEXIS 110273, at *72. For the

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21/ Prescription warning labels containing an FDA-mandated black box warning are particularly subject to being deemed adequate as a matter of law. *See, e.g., In re: Chantix (Varenicline) Prods. Liab. Litig.*, 881 F. Supp. 2d 1333, 1340 (N.D. Ala. 2012); *Hain v. Johnson & Johnson*, No. ATL-L-8568-11 MT, at 6-11 (N.J. Sup. Ct. 2013) (Ex. A) ("Courts have previously held prescription warning labels containing a boxed warning, mandated by the FDA, are adequate as a matter of law.").

same reasons, this Court should grant summary judgment to Defendants on Plaintiff's failure to warn claim.

Courts have also held that FDA-approved warnings that expressly warn of the precise injury suffered by a plaintiff, and the consequences of suffering that injury, are adequate as a matter of law. *McDowell*, 58 F. Supp. 3d at 403; *Gaynor*, 2014 U.S. Dist. LEXIS 82003, at *33-34; *Banner v. Hoffman-La Roche Inc.*, 891 A.2d 1229, 1237-38 (N.J. Super. Ct. App. Div. 2006) (applying the *Martin* test, the court found warnings that are accurate, clear, and unambiguous to convey the risk are adequate as a matter of law); *see Alston*, 670. F. Supp. 2d at 284 (S.D.N.Y. 2009); *see also Fane v. Zimmer, Inc.*, 927 F.2d 124, 130 (2d Cir. 1991). In *McDowell*, the plaintiff claimed that the label for the prescription drug Cymbalta misled medical professionals about the rate of discontinuation symptoms by listing the events seen in the clinical trials "at a rate greater than or equal to 1%." *McDowell*, 58 F. Supp. 3d at 395. The plaintiff argued that although the label warned of the specific risk at issue, physicians were misled and that withdrawal symptoms actually occurred in 44-50% of Cymbalta patients who discontinued the drug after nine weeks. *Id*. The court rejected the plaintiff's claim and refused to graft onto the adequacy standard a requirement that a drug label include specific adverse event frequencies. *Id.* at 405-406. Instead, the court held that the Cymbalta warning was adequate as a matter of law because it warned of the "specific malady" suffered by the plaintiff, was "accurate, clear, consistent on its face," and "portray[ed] with sufficient intensity the risk involved in taking the drug." *Id.* at 406 (citation omitted). The Court should reach the same conclusion here.

D. *Defendants Are Entitled to Summary Judgment Because Without Competent Expert Testimony from a Neurologist on the Alleged Inadequacy of the FDA-Approved Label, Plaintiff Cannot Prove the Label was Inadequate.*

1. Plaintiff's Expert Does Not Opine About the Adequacy of the Tysabri Label.

Plaintiff's Complaint asserts multiple causes of action, but the crux of all of Plaintiff's claims is that Tysabri's labeling failed to adequately warn of the three risk factors that Defendants determined over time increased the risk of PML.[22/] *See, e.g.,* Compl. ¶ 71. Given the complexities of the medical issues, and because Tysabri's labeling contains extensive PML warnings, Plaintiff cannot prove a failure to warn claim without competent and relevant expert testimony from a physician, in this case a neurologist who treats MS. Expert opinion testimony from a neurologist is necessary because a lay jury could not possibly determine the adequacy of the extensive PML warnings based on the jurors' common experience. *Christison,* 2016 U.S. Dist. LEXIS 110273, at *62-63 ("A lay jury would not be able to determine by calling upon their own life experiences and would be speculating in making findings about the adequacy of the Tysabri warning label, which warned extensively about PML. Therefore, there must be expert testimony that the [defendant's conduct] probably caused the injury.") (internal citations and quotations omitted); *see also Fane*, 927 F.2d at 131 (applying New York law) ("Absent competent medical expert testimony on the issue of causation, [plaintiff] could not prove the elements of a cause of action based in strict products liability or negligence"). Courts have recognized that expert testimony is particularly appropriate when the manufacturer does provide some warning, in order to determine the adequacy of that warning. *See Mulhall v. Hannafin,* 841 N.Y.S. 2d 282, 286-87 (N.Y. App. Div. 2007); *see also Gentile,* 2016 Mass. Super. LEXIS 238,

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22/ The Plaintiff's causes of action include claims for negligence, strict products liability, failure to warn, negligent misrepresentation, breach of implied warranty, and wrongful death. All are based on the alleged failures to warn.

at *18 ("When evaluating failure to warn claims, the court must always bear in mind that the warning is to be read and understood by physicians, not laypersons. Because the adequacy of the warnings cannot be evaluated by a layperson, expert testimony is necessary to resolve the issue.") (internal citations and quotations omitted). Simply put, Plaintiff cannot satisfy his burden of proof on a failure to warn claim because he does not have expert testimony from a physician.

As the *Christison* and *Gentile* courts held based on the same expert report and expert testimony, Plaintiff's sole liability expert, Eugene Major, Ph.D. ("Major"), does not opine anywhere in his report or in his deposition testimony on the adequacy of the extensive PML warnings in the Tysabri labeling and is, in any event, not qualified to do so.[23/] Major does not use the words "warning" or "label" anywhere in his report, and he never describes the language that he contends should have been in the label to make it adequate. (SF ¶ 135).[24/]

Major also offers no testimony concerning duration of treatment or prior immunosuppressant treatment that would support a failure to warn claim on those two risk

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23/ Major's deposition testimony is the same in this case as in *Christison* and *Gentile*. Defendants deposed Major once, and the parties agreed that the testimony applies in this case. The Parties agreed that "each expert disclosed by the Parties will be deposed only once," and, thus, Dr. Major's testimony in *Christison* also applies in this case. 2016 U.S. Dist. LEXIS 110273; Letter from Yalonda T. Howze, Esq., attorney, Mintz, Levin, Cohn, Ferris, Glovsky, and Popeo P.C., to Edward Blizzard, Esq., attorney, Blizzard & Nabers, LLP, (August 13, 2015) (on file with author).

24/ The crux of what Major says in his report and deposition testimony is that Defendants should have informed doctors and their patients (through the TOUCH Program), that JCV causes PML, and only patients who have been exposed to JCV can get PML. Major asserts that this information "might" have been useful. Defendants' duty, however, is to warn the physician, so Major's opinion as to what Defendants should have told patients directly is irrelevant. *Gentile*, 2016 Mass. Super. LEXIS 238 at *19-20 (finding that Major's statement that a JCV antibody test "might" be useful in helping to assess a higher risk of PML does "not support an argument that the warnings were inadequate to caution a physician that a risk of PML existed."). Moreover, as Major admitted, a neurologist treating MS with Tysabri would be expected to know the basic biologic fact that PML is caused by JCV. Defendants have no duty to instruct physicians on basic medical knowledge or how to practice medicine. *Spychala v. G.D. Searle & Co.*, 705 F. Supp. 1024, 1031-32 (D.N.J. 1988).

factors. Although Major asserts that Biogen could have developed an anti-JCV antibody assay earlier, he offers no testimony that Defendants had sufficient data that anti-JCV antibodies could be a biomarker to predict increased PML risk. In fact, FDA determined that the data were not sufficient to support a labeling change concerning the significance of anti-JCV antibodies until January 2012, after Mrs. Amos's PML diagnosis. *See Christison*, 2016 U.S. Dist. LEXIS 110273, at *78-82.

In *Christison*, the court granted summary judgment to Biogen and Elan on each cause of action "due to [plaintiff's] failure to provide expert testimony regarding causation and the adequacy of the Tysabri label." 2016 U.S. Dist. LEXIS 110273, at *66. Similarly, in *Gentile*, the court found that "plaintiff has failed to provide evidence establishing that a genuine issue of material fact exists regarding the adequacy of the warnings." 2016 Mass. Super. LEXIS 238, at *18. The court decided that "[b]ecause Dr. Major's testimony does not create a dispute of material fact regarding whether Tysabri's warnings were adequate to convey to a prescribing physician the risk of developing PML, plaintiff has failed to establish an entitlement to relief on his failure to warn claim." *Id.* at *20.

2. Plaintiff's Expert is Not Qualified to Opine About the Adequacy of the Tysabri Label.

Major is also not qualified to opine on the adequacy of Tysabri's PML warnings, as detailed in the accompanying *Daubert* motion. In fact, Major testified that he is not a medical doctor, that he does not know the requirements of drug labeling, and that he is not qualified to and will not offer any opinions concerning the adequacy of Tysabri's label:

> Q. And could the drug company say anything in its labeling about the use of such assays in connection with prescribing a drug?
>
> A. You know, I – I'm not qualified to answer what goes on labeling of a prescription drug.

(SF ¶¶ 129, 130; s*ee also* Def. Ex. 15).

> Q. Is it your belief that Biogen Idec and Elan should have recommended to physicians in the labeling that they do antibody testing?
>
> A. It was certainly my recommendation that many steps be taken to understand what's going on in these patients. I'm not going to comment on the labeling.

(*Id.*).

Based on this testimony, the *Christison* court held: "It could not be clearer. Dr. Major himself stated that he is not qualified to answer what goes on labeling of a prescription drug." *Christison*, Dkt. 195, at 5 (internal quotations omitted); *see also Christison*, 2016 U.S. Dist. LEXIS 110273, at *64 (plaintiff "does not have a qualified expert to testify on what 'a more adequate label' would contain"). In *Gentile*, the court also found on this record that Major (1) is not familiar with the requirements for labeling for prescription drugs; (2) is not a medical doctor; (3) does not have the qualifications necessary to opine on matters of treating patients; and (4) does not assert that he has the experience necessary to interpret warnings from the perspective of a prescribing physician. 2016 Mass. Super. LEXIS 238, at *20. Thus, "even if Dr. Major were prepared to testify about the adequacy of the warnings, his opinion would be inadmissible." *Id*; *see e.g., Calisi*, 2013 U.S. Dist. LEXIS 139257, at *26-27 (holding an expert unqualified because he "is not a medical doctor and does not have qualifications to opine on what is clinically appropriate in terms of treating patients") (quotations omitted); *see also Fane*, 927 F.2d at 132.

The only expert opinion on the adequacy of the PML warnings in this case is the sworn expert disclosure and deposition testimony of Defendants' expert Dr. Ellen Lathi, head of the Elliot Lewis Center for Multiple Sclerosis Care. Dr. Lathi is a highly experienced neurologist and MS treatment specialist who currently prescribes Tysabri in her practice. Dr. Lathi prescribed Tysabri at the time Mrs. Amos was being prescribed the drug, and Dr. Lathi confirms

that the Tysabri warnings were at all times adequate to inform physicians of the PML risk. *See* Lathi Expert Report. (Def. Ex. 22). Major does not contest this opinion. In fact, he testified he would defer to the opinions of physicians with respect to clinical decision-making issues. (SF ¶ 128; *see also* Def. Ex. 15).

Plaintiff has not presented any expert testimony that would support a jury finding in Plaintiff's favor on any of the dispositive issues in this case, and Major is not qualified to render such an opinion in any event. Without such testimony, Plaintiff cannot establish a *prima facie* case on a failure to warn claim and Defendants are entitled to judgment as a matter of law.

3. Dr. Major's Opinion Concerning Communication of Assay Information to Physicians and Patients Through the TOUCH Program and Development of an Assay is Not Relevant to Any Claim in this Case.

Rather than opining about the sufficiency of the PML warnings, Major simply states that an antibody assay could have been developed earlier, made available to patients through the TOUCH Program, and that a positive result would be "useful" information to patients and physicians. (SF ¶ 136; *see also* Def. Ex. 15). Major's opinion is not relevant to any claim in the case.

First, the assertion that an antibody assay could have been developed earlier is made only in Major's expert report; none of the counts in the Complaint include this liability theory.

Second, the issue before the Court is not whether the results of an anti- JCV antibody test would be "useful," but whether the alleged failure of a manufacturer to inform physicians of the significance of that information renders the PML labeling *inadequate* and the drug "unreasonably dangerous." Dr. Major offers no expert testimony on those critical points. *Cf. In re Chantix*, 881 F. Supp. 2d 1333, 1341-42 (N.D. Ala. 2012) (although one "of plaintiffs' experts, does state that in his opinion, Chantix should not be used as a first line treatment," where that same expert did not opine that "the 2009 warning contained in the Chantix label was

inadequate," summary judgment was appropriate.). Whether a physician would find antibody information "useful" has nothing to do with the adequacy of the Tysabri PML warnings because the warnings presume a patient is or could become infected with the JC virus—a necessary predicate for PML.

Contrary to Major's contention, informing a physician that a patient is JCV antibody positive, with no statistically significant data as to what that means in terms of individual PML risk, adds nothing to the label.[25/] To suggest without data that a negative finding means lower PML risk would greatly weaken the unqualified black box label by stating, without knowing, that an identifiable group of patients (those who test negative) are actually at low or lower risk.[26/]

Third, the undisputed record contradicts Major's theory. FDA prohibited Defendants from changing the TOUCH program without FDA approval, stating in its June 5, 2006 reapproval letter that "[a]ny change to the [TOUCH] program must be discussed with FDA prior to its institution …." (SF ¶ 46). In September 2010, FDA rejected Biogen's proposal to add information to the Tysabri labeling regarding the significance of anti-JCV antibodies. (SF ¶ 108). In November 2010, FDA rejected Biogen's proposal to make the Biogen-developed JCV antibody assay available to Tysabri prescribers as an LDT. (SF ¶ 111); *see also* Section II, *infra*.

Fourth, Defendants had no independent legal obligation to develop and "commercialize" an assay. Major's assertion that Defendants had a state law *duty* to develop and "commercialize"

25/ The September 2010 FDA meeting minutes also confirm that FDA agreed a positive JCV antibody finding, in the absence of sufficient data related to PML risk, would not affect the unqualified PML warning because "[i]t is not clear how these results would guide therapy in antibody positive patients." (SF ¶ 109).

26/ Dr. Major agreed that without studies with adequate data, the relationship between a negative finding on a JCV antibody assay and a patient's risk of PML cannot be determined. (SF ¶140; *see also* Def. Ex. 15). He agreed, for example, that it was possible based on what was known at the time that persons exposed to JCV for the first time ("primary infection") while on immunomodulatory therapy could actually be at *higher* risk of developing PML than those who have antibodies to the virus. (SF ¶ 140; *see also* Def. Ex. 15).

a separate non-drug product (a JCV antibody assay) for use in connection with an FDA-approved medication (Tysabri) is wholly unsupported by law. It is a basic legal principle that a plaintiff cannot recover in a tort action without first establishing that the defendant owed the plaintiff a legally cognizable duty, the breach of which caused the claimant's injury. *See, e.g., Colon v. BIC USA, Inc.*, 199 F. Supp. 2d 53, 82 (S.D.N.Y. 2001). A pharmaceutical manufacturer's duty, as established by law, is to adequately warn physicians of the drug's known risks. *McDowell*, 58 F. Supp. 3d at 402.[27/] Plaintiff cannot point to any case where a court has ever imposed liability on a drug company based on the failure to develop and commercialize an entirely separate non-drug product (such as an assay, test, or diagnostic product) to develop information for use with the manufacturer's FDA-approved drug.[28/] Simply put, if Defendants are to be held liable to Plaintiff on a product liability theory, it can only be a liability based on failure to warn, a claim for which Plaintiff has offered no expert support.

[27/] In *Christison*, the court determined that a manufacturer's duty is to engage in reasonable conduct, and the question regarding duty is not whether they have an obligation to engage in a specific act. 2016 U.S. Dist. LEXIS 110273, at *76. New York law, however, limits a drug manufacturer's duties (to the extent they arise out of the sale of a product) to reasonableness in the design, manufacture, and warning associated with the product. *McDowell*, 58 F. Supp. 3d at 410-11. In an analogous context, claimants have sought recovery on the theory that a drug company has an independent duty to conduct certain tests or clinical trials. Courts uniformly hold that no such duty exists independent of a product manufacturer's legally-imposed duties related to product design, manufacture, and warnings. *See, e.g., Vassallo v. Baxter Healthcare Corp.*, 428 Mass. 1, 19 (1998) ("[E]vidence of failure adequately to test a product is relevant to claims of design, manufacturing, or warning defects, but does not furnish a separate, independent basis of liability."); *Tompkins v. R.J. Reynolds Tobacco Co.*, 92 F. Supp. 2d 70, 91 (N.D.N.Y. 2000) (granting summary judgment against "negligent failure to test," as it relates either to warning or design defect claims and satisfies neither); *Skotak v. Tenneco Resins., Inc.*, 953 F.2d 909, 912 n.5 (5th Cir. 1992) (applying Texas law) (Plaintiffs' "negligence claims, such as the alleged failure to adequately test [the product], are subsumed within" a failure to warn claim.); *Jones v. Ortho Pharm. Corp*, 163 Cal. App. 3d 396, 406 (Cal. App. 1985) (refusing to "presume that had defendant conducted the clinical studies plaintiff contends should have been done, those studies would have established" causation).

[28/] *Back v. Wickes*, 375 Mass. 633, 643 (1978) (holding the correct standard of care in a negligence claim as "the standard of the ordinary, reasonably prudent manufacturer in like circumstances."); *see Fane*, 927 F. 2d at 130 (2nd Cir. 1991) (applying New York law).

E. *Plaintiff Cannot Establish Proximate Cause Because Plaintiff has Failed to Meet His Burden of Proving that Drs. Smith and Medved Would Not Have Prescribed the Drug Had the PML Warnings Been Different.*

Plaintiff has the burden of proving both that Tysabri's warnings were inadequate *and* that the inadequacy of the label proximately caused the harm: if the warnings had been different, the physicians' prescribing decisions would have been different and Plaintiff's PML and death would have been avoided. *See, e.g., DiBartolo v. Abbott Labs.*, 914 F. Supp. 2d 601, 611-12 (S.D.N.Y. 2012) (the alleged warning defect must be the proximate cause of plaintiff's injury); *see also McDowell*, 58 F. Supp. 3d at 408; *Mulhall,* 841 N.Y.S. 2d at 287 ("[P]laintiffs had to show that had the warning been different, Dr. Hannafin would have departed from her normal practice and used another device."); *Alston*, 670 F. Supp. 2d at 285. Summary judgment is appropriate where a plaintiff fails to establish that a prescribing physician's decision to prescribe a particular medication would have changed if a different warning had been given. *McDowell*, 58 F. Supp. 3d at 408.[29/] Here, Plaintiff cannot prove proximate cause for several reasons.

First, there is no affirmative testimony in this case from any of the prescribing physicians that they would have done anything differently had the labeling included information earlier

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29/ Jurisdictions across the country apply a similar standard and routinely dismiss such cases. *See, e.g., Eck v. Parke, Davis & Co.*, 256 F.3d 1013, 1024 (10th Cir. 2001) ("[Plaintiffs] are unable to demonstrate that a warning would have changed Dr. Rodgers' or Dr. Newey's behavior at the time of prescribing Dilantin and Isocet, respectively."); *Odom v. G.D. Searle & Co.*, 979 F.2d 1001, 1003 (4th Cir. 1992) ("Even viewing the facts most favorably to [the plaintiff], we cannot escape the district court's conclusion that [the doctor] would have prescribed the [product] no matter how carefully Searle refined the phrasing of its warning."); *In re Norplant*, 215 F. Supp. 2d 795, 829 (E.D. Tex. 2002) (stating that plaintiffs must show that a different warning "would have changed the decision of the treating healthcare provider so that he or she would not have prescribed [the drug]."); *See also Willet v. Baxter Int'l., Inc.*, 929 F.2d 1094, 1098-99 (5th Cir. 1991); *Miller v. Pfizer Inc.*, 196 F. Supp. 2d 1095, 1127-28 (D. Kan. 2002); *Dyer v. Danek Med., Inc.*, 115 F. Supp. 2d 732, 741-42 (N.D. Tex. 2000); *Dyson v. Winfield*, 113 F. Supp. 2d 35, 41 (D.D.C. 2000); *Lawson v. Smith & Nephew Richards, Inc.*, No. 4:96-cv-0297, 1999 U.S. Dist. LEXIS 18922, at *17-18 (N.D. Ga. Sept. 30, 1999); *Woulfe v. Eli Lilly & Co.*, 965 F. Supp. 1478, 1485-86 (E.D. Okla. 1997).

about duration of treatment, prior immunosuppressant use, and the significance of a positive or negative anti-JCV antibody test (unsupported by data).

Second, it is undisputed that Drs. Smith and Medved were aware of the PML risk when they prescribed Tysabri and they discussed the risk with Mrs. Amos. (SF ¶¶ 63, 75). They testified that the labeling adequately warned of the PML risk to permit them to prescribe the drug safely. (SF ¶¶ 67).

Third, even if the warnings included the PML risk factors that Plaintiff now claims should have been in the label, Mrs. Amos's physicians would still have prescribed the drug. In fact, they did. Dr. Smith continued to prescribe Tysabri to Mrs. Amos after the label was updated to include the risk of duration of treatment. (SF ¶ 66). He also continued to prescribe Tysabri to Mrs. Amos after the label was updated to include the risk of prior immunosuppressant use (SF ¶ 111), and Mrs. Amos had no history of prior immunosuppressant use in any event (SF ¶ 69). Dr. Smith independently concluded, before the label was updated, that a positive JCV antibody result meant an increased risk of PML. (SF ¶ 120).[30/] He enrolled Mrs. Amos in the STRATIFY II clinical trial and, in August 2010, she tested positive for the presence of anti-JCV antibodies using the Biogen-developed assay. (SF ¶ 121). After her positive test, Dr. Smith continued to prescribe Tysabri to Mrs. Amos.

Moreover, Dr. Medved and Physician Assistant Yehl both testified that all three PML

30/ "Under New York law, where the treating physician is independently aware of potential adverse events, that knowledge is an intervening event relieving the manufacturer of any liability to a patient under the failure to warn theory." *McDowell*, 58 F. Supp. 3d at 406 (quoting *Banker v. Hoehn*, 718 N.Y.S.2d 438, 440-41 (N.Y. App. Div. 2000) (internal quotations omitted); *Alston*, 670 F. Supp. 2d at 286 ("The Plaintiff has not shown that a failure to warn… was the proximate cause of his injuries, as his physicians were aware of the risks…"); *See also Odom*, 979 F.2d at 1003 ("[T]he manufacturer cannot be said to have caused the injury if the doctor already knew of the medical risk."); *Carnes v. Eli Lilly, Co.*, No. 0:13-591-CMC, 2013 U.S. Dist. LEXIS 176201, at *21-22 (D.S.C. Dec. 16, 2013) (physician's independent knowledge of potential symptoms made it impossible for plaintiff to establish proximate cause).

risk factors were known to them when they prescribed Tysabri to Mrs. Amos in June 2011. (SF ¶¶ 122-126).[31/] The risks associated with duration of treatment and prior immunosuppressant use were included in Tysabri's PML warnings at that time, and they knew that Mrs. Amos had been on Tysabri for more than two years and had not taken any prior immunosuppressant drugs. (SF ¶¶122-123). Dr. Medved and Brandon Yehl both testified that they knew when they prescribed Tysabri to Mrs. Amos that the presence of anti-JCV antibodies put a patient at higher risk for PML and that Mrs. Amos had tested positive for anti-JCV antibodies. (SF ¶ 123). As a result, Plaintiff's claim that Defendants failed to warn about these PML risk factors must fail.

F. *Plaintiff's Remaining State Law Claims are Subsumed within the Warnings Claim and Defendants are Entitled to Summary Judgment on Those Claims as a Matter of Law Based on the Adequacy of the PML Warnings.*

There is no evidence in the undisputed record supporting Plaintiff's laundry list of subsidiary claims such as negligence, negligent misrepresentation, strict liability, breach of implied warranty, and wrongful death. Moreover, these claims are an attempt to create duties that do not exist and must fail in the face of Tysabri's legally adequate warning. Under New York law, a manufacturer's duty to users of its product is determined by product liability principles. The other claims in this case all relate to the Tysabri labeling and the TOUCH Program, and they are simply an attempt by the Plaintiff to avoid judgment under the learned intermediary doctrine. In the absence of a direct relationship between the manufacturer and the Plaintiff, a plaintiff cannot avoid the learned intermediary doctrine by framing his claim as breach of implied warranty, negligent misrepresentation, or some other alternative cause of action. *See, e.g., Prohaska v. Sofamor, S.N.C.*, 138 F. Supp. 2d 422, 447 (W.D.N.Y. 2001) ("[S]ince only a doctor can prescribe and use [the medical device], any reliance on [the manufacturer's] statements that

31/ Dr. Medved testified that he would take the majority of patients who had all three PML risk factors off Tysabri. (SF ¶ 126). Mrs. Amos did not have all three risk factors.

[the plaintiff] could possibly claim is eliminated by the learned intermediary rule."). For that reason, courts routinely dismiss these tag-along claims based on a finding that the warnings were adequate. *See, e.g.*, *In re Norplant*, 955 F. Supp. 700, 709 (E.D. Tex. 1997) (stating that "[i]f the [learned intermediary] doctrine could be avoided by casting what is essentially a failure to warn claim under a different cause of action . . . then the doctrine would be rendered meaningless.").

The adequacy of the Tysabri warning label, as a matter of law, precludes any related claims for negligence, negligent misrepresentation, strict liability, breach of warranty, or wrongful death. *Gentile*, 2016 Mass. Super. LEXIS 238, *24-25 ("[U]nder New York law, where a failure to warn claim cannot succeed, the court must dismiss any related claims for negligence, strict liability, breach of warranties, or fraud."); *McDowell*, 58 F. Supp. 3d at 410-411; *see also Gaynor*, 2014 U.S. Dist. LEXIS 82003, at *34-36 (applying New York law); *In re Accutane Prods. Liab.*, MDL 1626, 2012 U.S. Dist. LEXIS 114701, at *21-22 (M.D. Fla. July 24, 2012) (applying New York law).

In addition, Defendants are entitled to summary judgment on Plaintiff's negligent misrepresentation claim on the independent ground that "privity does not exist between manufacturers and patients when the medication is only available by prescription." *Becker v. Cephalon, Inc.*, No. 14 Civ. 3864, 2015 U.S. Dist. LEXIS 123670, at *22-23 (S.D.N.Y. Sept. 15, 2015); *see also DiBartolo*, 914 F. Supp. 2d at 623-24.

G. *Defendants are Entitled to Summary Judgment on All Claims Regarding Anti-JCV Antibodies Because They are Preempted by Federal Law, as Two Courts Have Held on an Identical FDA Record.*

1. Plaintiff's Claims are Preempted Because Defendants Could Not Have Warned About JCV Antibodies and Could Not Have Made an Assay Available Without FDA Approval.

The Supremacy Clause of the United States Constitution provides that in the event of a conflict, federal law preempts any state law that conflicts with the exercise of federal power.

U.S. CONST. art. vi, cl. 2. The U.S. Food, Drug, and Cosmetics Act, and related federal regulations, do not expressly preempt state tort law, including failure to warn and other product liability claims. *Wyeth v. Levine*, 555 U.S. 555, 581 (2009). However, when the plaintiff's liability theory in a particular case is based on an argument that the drug manufacturer had a state tort law duty to do something that could not lawfully be done independently by the drug company under federal law, *i.e.*, without the permission of the FDA, "conflict preemption" bars the state law or claim. *See, e.g.*, *Mut. Ins. Co. v. Bartlett*, 133 S.Ct. 2466, 2473 (2013).

When FDA approves a drug, it also approves both the drug and the labeling that accompanies that drug and manufacturers need to seek FDA approval before making any major changes to the FDA-approved label. *Bartlett*, 133 S. Ct. at 2471 (citing 21 C.F.R. § 314.70(b)(2)(i)). Certain FDA regulations, however, known as the Changes Being Effected ("CBE") regulations, create a regulatory pathway by which drug manufacturers can unilaterally make certain non-major changes to their product labels without prior FDA approval. To qualify for use of this regulatory pathway, the label change must: (1) "reflect newly acquired information"; and (2) accomplish one of five objectives listed in the regulation. 21 C.F.R. § 314.70(c)(6)(iii).[32/]

In *Levine*, the Supreme Court held that "conflict" or "impossibility" preemption did not apply where the drug manufacturer had the right under the CBE regulations to unilaterally change the label (without advance FDA permission) to reflect newly available safety information and because Wyeth offered no "clear evidence" that the FDA *would have* rejected such a

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32/ FDA defines "newly acquired information" narrowly: newly acquired information means data, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (*e.g.* meta-analyses) if the studies, events or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA. 21 C.F.R. § 314.3(b).

proposed change. *Levine*, 555 U.S. at 568; 21 C.F.R. § 314.70. Two years later, the Supreme Court held in *PLIVA v. Mensing* that a generic drug manufacturer could not be held liable on a failure to warn claim because only the branded drug company had the legal right to change or propose changes to an FDA-approved label. 564 U.S. 604, 623-25 (2011). More recently, in *Bartlett*, the Supreme Court held that a drug manufacturer, *whether a generic or a brand-name manufacturer*, could not be liable for a defect in the design of a product unless the drug company could unilaterally change the design without FDA review and approval. *Bartlett*, 133 S.Ct. at 2471.

In *In re Celexa and Lexapro Mktg. and Sales Practices Litig.*, 779 F. 3d 34, 40 (1st Cir. 2015), the First Circuit held, based on *Levine* and its progeny, that if the CBE process is *not* available to the defendant to change the initial FDA-approved labeling (as, for example, when the label change would not be based on "newly-acquired" information), state law failure to warn claims based on alleged inadequacies in the drug's FDA-approved labeling are preempted. In other words, a drug company cannot change the initial FDA-approved warnings unless it has both newly acquired information and a legal avenue to change the label through the CBE regulations. As explained by the First Circuit, "the line so drawn lets FDA be the exclusive judge of safety and efficacy based on information available at the commencement of marketing, while allowing the states to reach contrary conclusions when new information not considered by FDA develops." *Id.* at 41; *see also Utts v. Bristol-Myers Squibb Co.*, et al, No. 16-cv-5668, 2016 U.S. Dist. LEXIS 178335, *30 (S.D.N.Y. Dec. 23, 2016) (finding preemption of failure to warn claims that were based on information presented to FDA at the time of the drug's approval and deciding that plaintiff could not act independently of FDA to update the drug's label).

Here, Plaintiff alleges during the time Mrs. Amos's neurologists prescribed Tysabri from July 2006 through June 2011, Defendants had a duty to warn patients that if they have anti-JCV antibodies they are at a higher risk of developing PML (*see, e.g.*, Compl. ¶ 123). Defendants could not lawfully have changed the Tysabri warning label without prior FDA approval based on adequate data.

The CBE regulations do not apply because a drug manufacturer cannot add or change a black box warning without prior Agency approval. 21 C.F.R. § 201.57(c)(1); 44 Fed. Reg. 37434, 37448 (June 26, 1979) ("[T]o ensure the significance of boxed warnings in drug labeling, they are permitted in labeling only when specifically required by FDA."); *Kaleta v. Abbott Labs.*, 87 F. Supp. 3d 916, 924 (Feb. 2, 2015); *see also* Jones Expert Report, pp. 6, 15-21, Decl. Ex. 78. (CBEs are not used to modify boxed warnings or to amend REMS programs).[33/] Thus, Defendants could not have used the CBE regulations to change Tysabri's black box warning regarding anti-JCV antibodies.

In addition, the CBE regulations do not apply to labeling changes based on information that was available to FDA when the drug was approved. *See Celexa*, 779 F. 3d at 41; FDA, CDER, *Guidance for Industry: Changes to an Approved NDA or ANDA*, 2004 WL 3199016, at *24 (April 2004); Jones Expert Report, pp. 19-21. Any change to the labeling or warnings must be based on information discovered, obtained, or as result of a re-analyses of data after the FDA's approval. *Celexa*, 779 F. 3d at 41.[34/]

[33/] Similarly, REMS programs like the TOUCH Program are creatures of discretionary Agency action that can only be added or changed on substantive matters with FDA approval. (SF ¶ 46). In this case, FDA made this clear in the marketing approval letter issued in connection with Tysabri's reintroduction to the market. (SF ¶ 46).

[34/] Major contends that all of the knowledge and techniques necessary to develop an anti-JCV antibody assay (and why in his view such an assay would potentially be significant) were available to Defendants and FDA by 2005. *See* Report of Major, Def. Ex. 24, at p. 10.

The record is bereft of any evidence that sufficient data were available to Defendants during the time Mrs. Amos was taking the drug.[35/] On the contrary, FDA was aware of the potential link between JCV antibodies and PML as early as 2006, and it asked Biogen to conduct an assessment for the presence of JCV antibodies for patients entering clinical trials. (SF ¶ 49). Biogen submitted a report to FDA, finding that there was no "consensus on a clinically relevant cutoff" for JCV antibody detection. (SF ¶ 35). FDA reapproved the drug without any mention of JCV antibody status in the label. (*See* SF ¶ 39). Moreover, the undisputed evidence is that more than three years later, in December 2009, a panel of U.S. regulatory experts determined that "data on the assay was too preliminary to be of predictive value" regarding PML at the time. (SF ¶ 104). In late 2010, FDA expressly rejected such changes to Tysabri's label and did not permit the labeling change until January 2012, after Biogen conducted two clinical trials, and after Biogen addressed numerous FDA questions (SF ¶¶ 110). Without sufficient new post-approval data, Biogen could not have used the CBE process to say anything about the significance of anti-JCV antibodies sooner. *See also Seufert v. Merck Sharp & Dohme Corp*., No. 13-cv-2169, 2016 U.S. Dist. LEXIS 91837, at *38 (S.D. Ca. May 11, 2016) (stating that any changes to product labeling would have to be supported by reasonable evidence of a causal association, and that it is a technical violation of federal law to propose a CBE that is not based on reasonable evidence). For these reasons, Plaintiff's claims are preempted under the Supreme Court's rulings in *Bartlett*

35/ During the time Mrs. Amos was treated with Tysabri there were no statistically significant data concerning the significance of anti-JCV antibodies in relation to PML risk. This fact is undisputed, and Major admitted this fact. (SF ¶ 95). Nor was there any way to know that the science would develop to the point where an assay could be validated and an assay result could be shown through clinical data to be useful to physicians in making treatment decisions. Plaintiff cannot use the successful *results* of Defendants' research efforts to retroactively impose an affirmative duty on Biogen to have warned about those research results earlier. Such a claim disregards the fundamental principle that a drug company's warning is judged based on the state of scientific knowledge at the time the drug was prescribed. *See*, *supra*, at p. 15-19.

and *Mensing* and the rationale of the First Circuit in *Celexa*.

2. Plaintiff's Claims Regarding Anti-JCV Antibodies are Preempted Because there is "Clear Evidence" that FDA Would Not Have Approved Any Such Labeling Changes Before 2012.

In *Levine*, the Supreme Court also held that when a drug manufacturer can show by "clear evidence" that FDA *would have* rejected a labeling change instituted by the manufacturer under the CBE regulation or otherwise, any state law tort claim based on the failure to make that change is preempted. 555 U.S. at 571-72; *see also Dobbs v. Wyeth Pharm.*, 797 F. Supp. 2d 1264, 1272-77 (W.D. Okla. 2011) (finding the claims preempted due to FDA's conclusion there was "no scientific evidence to support a causal connection between SSRI's and suicidality" warranting an enhanced warning"). After *Levine*, numerous courts have rejected failure to warn claims against prescription drug manufacturers where there is "clear evidence" in the regulatory record that FDA would not have approved a proposed warning.[36/]

The undisputed record in this case shows that FDA explicitly rejected inclusion of antibody testing information in Tysabri's label just months before Mrs. Amos stopped taking Tysabri, and that FDA would not permit the labeling change until after she stopped taking Tysabri. (SF ¶¶ 108, 111). As noted, in September 2010, FDA rejected Biogen's proposal to add information to the label concerning anti-JCV assay antibodies, finding that the limited information (17 pre-PML samples) available concerning the correlation between a positive antibody finding and PML was not enough data to justify a label change. (SF ¶ 108). FDA also decided that the number of cases was too small, the samples were obtained retrospectively and it

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[36/] *See, e.g.*, *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 873 (7th Cir. 2010); *Cerveny v. Aventis, Inc.*, No. 2:14-cv-00545, 2016 U.S. Dist. LEXIS 34182 (D. Utah March 16, 2016); *In re: Incretin-Based Therapies Prods. Liab. Litig.*, 142 F. Supp. 3d 1108, 1132 (S.D. Cal. 2015); *Rheinfrank v. Abbott Labs., Inc.*, No. 1:13-cv-144, 2015 U.S. Dist. Lexis 104564 (S.D. Ohio Aug. 10, 2015); *Kaleta v. Abbott Labs, Inc.*, 87 F. Supp. 3d 916, 924 (S.D. Ill. 2015) (ruling on motion in limine); *Glynn v. Merck Sharp & Dohme Corp.* (*In re Fosamax Prods. Liab. Litig.*), 951 F. Supp. 2d 695, 703 (D.N.J. 2013).

was "too early" to support the methodology. (SF ¶ 109).[37/] In November 2010, FDA also rejected Biogen's proposal to make the anti-JCV assay available to physicians based on FDA's determination that "[t]he usefulness of this test in treatment with Tysabri has not been established." (SF ¶ 111). After Biogen obtained more data and submitted it to FDA in October 2011, after Mrs. Amos's PML diagnosis, FDA approved the label change in January 2012.

FDA's refusal until January 2012 to permit labeling concerning the assay and the significance of JCV antibodies based on the insufficiency of the available data to demonstrate "clinical utility," is "clear evidence" that FDA would not have permitted a label change earlier, during the time period in which Mrs. Amos was being treated with the drug. In fact, it is conclusive evidence.

For this reason, the *Christison* and *Gentile* courts held, on the identical FDA regulatory record as in this case, that claims challenging the adequacy of the PML warnings based on the failure to discuss antibodies are preempted. In *Christison*, the court held that FDA would not have approved a change to the Tysabri label regarding JCV antibodies ***until 2012***—more than six months after Mrs. Amos's PML diagnosis. The court explained:

> The FDA was aware of the potential link between JCV antibodies and PML as early as 2006, but the FDA did not approve changes to the Tysabri label regarding JCV antibodies until 2012. The Companies are correct that "[i]f 17 Tysabri-association pre-PML samples were insufficient to persuade FDA in 2010 of the predictive value of antibody testing in connection with PML risk stratification, there clearly would not have been sufficient data more than two years earlier . . . " Accordingly, there is "clear evidence" that the FDA would not have approved a change to the Tysabri label prior to Mrs. Christison's death, and the causes of action that Mr. Christison raises in this matter—negligence; negligent failure to warn; and negligent misrepresentation—which are based in state law, are

37/ Major acknowledged that the only way to correlate an antibody finding to PML risk was to have a sufficient number of pre-PML blood samples, preferably prospectively obtained (to have a more "robust" finding) (*see* SF ¶ 140; *see also* Def. Ex. 15), and that the number of PML cases/samples prior to 2010 was insufficient to draw any conclusions. Indeed, he estimated that it would take about 100 cases to obtain a useful statistical result. *Id.*

> preempted by federal requirements mandating FDA approval of changes to a drug's warning label.

Christison, 2016 U.S. Dist. LEXIS 110273, at *81-82.

Similarly, in *Gentile*, the court held that "FDA's decision to reject the proposed modifications regarding risks associated with providing Tysabri to patients with the JCV antibody demonstrates that prior to [plaintiff's] diagnosis, defendants could not have strengthened their warnings to comply with state law without violating the FDA's decision." 2016 Mass. Super. LEXIS 238, at *26. Indeed, the court found that "FDA rejected defendants' proposed change in the warning not because of the language used, but because the supporting data was not yet sufficiently persuasive." *Id*. at *27.

The reasoning in *Christison* and *Gentile* is supported by a number of closely analogous cases where courts have held that failure to warn claims against brand-name prescription drug manufacturers are preempted because of "clear evidence" that FDA would not have approved the labeling change argued by plaintiff, even if it had been unilaterally made by the drug company through a CBE.[38/] *See, e.g.*, *Rheinfrank*, 2015 U.S. Dist. LEXIS 104564, at *31; *Kaleta*, 87 F. Supp. 3d at 924 (ruling on motion in limine). The *Rheinfrank* court's rationale applies with equal force here:

> The Court finds that there is clear evidence that the FDA would not have approved a change to the 1999 label to include a warning of developmental delay . . . . Abbott tried, on various occasions, to secure approval of a developmental delay warning and its requests were twice denied by the FDA. In light of the fact that the FDA rejected the developmental delay warning in 2006 because it did not find that the available scientific evidence at that time supported the addition of such a warning, it is highly unlikely that the available scientific evidence, seven years prior to that date in 1999, would have supported the addition of such a

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[38/] Although "clear evidence" is a fact-specific standard, this body of case law demonstrates a developing bright-line rule regarding "clear evidence" after *Levine*: a warning change rejected by the FDA for lack of scientific evidence is "clear evidence" that this change would have also been rejected at any earlier date, thus a claim based on the rejected warning is preempted.

> warning. Notably, the FDA did not actually approve this developmental delay language until 2011.

Id. at *31-32 (citation omitted); *see also In re: Byetta* Cases, No. JCCP 4574, (Ca. Sup. Ct. Nov. 13, 2015); *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861, 873 (7th Cir. 2010); *Cerveny*, 2016 U.S. Dist. LEXIS 34182, at *31, 35; *Seufert*, 2016 U.S. Dist. LEXIS 91837, at *11, 35-40; *In re: Incretin-based Therapies Prods. Liab. Litig.*, 142 F. Supp. 3d at 1132; *In re Fosamax*, MDL No. 2243, 2014 U.S. Dist. LEXIS 42253, at *56-57 (D.N.J. March 26, 2014).

Because FDA rejected Biogen's proposed label change regarding the significance of anti-JCV antibodies in 2010, and did not allow this change until January 2012, after Mrs. Amos's PML diagnosis, there is conclusive evidence that FDA would not have approved the change earlier. The claim is preempted.

H. *Elan was Not the Application-Holder for Tysabri and Had No Legal Right to Initiate a Labeling Change or to Seek FDA Approval for Such a Change; the Failure to Warn Claims Against Elan are also Preempted on that Ground.*

Elan is entitled to summary judgment on Plaintiff's warnings claims on the additional independent preemption ground that it was not the holder of the approved Tysabri application and thus had no legal authority or ability to unilaterally change the Tysabri labeling. (SF ¶ 6). Under federal law, "[a] brand-name manufacturer seeking new drug approval is responsible for the accuracy and adequacy of its label." *Mensing*, 564 U.S. at 613 (*citing* 21 U.S.C. §§ 355(b)(1), (d)); *Levine*, 555 U.S. at 570-71. Federal regulations state that "the holder of an approved application" may make changes to "add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under 201.57(c) of this chapter." 21 C.F.R. § 314.70(c)(6)(iii)(A) (2006) (emphasis added).

Biogen is the holder of the approved application for Tysabri in the United States and is responsible by law and by its agreement with Elan for pharmacovigilance activities in the United States and Elan acts as the distributor. (SF ¶ 24). Because Elan is not the "holder of an approved application" (the NDA), Elan cannot unilaterally effect any changes to Tysabri's label. To paraphrase one Court's explanation of the rule, "a contractual relationship between [Biogen and Elan] cannot change the fact that [Elan] is not the NDA holder." *In re Fosamax Prods. Liab. Litig.*, No. 3:08-cv-00008, 2012 U.S. Dist. LEXIS 5817, at *26-28 (D.N.J. Jan. 17, 2012); *see Brazil v. Janssen Research and Develop. LLC*, No. 4:15-cv-0204-HLM, 2016 U.S. Dist. LEXIS 93528, at *33 (N.D. Ga, July 11, 2016) (dismissing plaintiff's claims premised on a failure to warn against a defendant that did not hold the NDA because "[w]hen a company does not have the NDA, it has 'no more power to change the label' of a drug than a generic manufacturer.") (*quoting In re Darvocet, Darvon, & Propoxyphene Prods. Liab. Litig.*, 756 F.3d 917, 940 (6th Cir. 2014)). Because Elan could not "independently do under federal law what [Plaintiff claims] state law requires of it," the state law failure to warn claims brought against Elan are preempted. *Mensing*, 564 U.S. at 620; *see Brazil*, 2016 U.S. Dist. LEXIS 93528, at *33 (same). The *Gentile* court granted summary judgment as to Elan for this reason as well. 2016 Mass. Super. LEXIS 238, at *28 ("Biogen is the holder of the original, approved application for Tysabri. Consequently, Elan could not have sought modifications of the label.").

IV. CONCLUSION

For all of the foregoing reasons, Defendants are entitled under Fed. R. Civ. P. 56 to the entry of final judgment in their favor and respectfully request that the Court enter summary judgment in Defendants' favor on Plaintiff's claim with prejudice, and grant Defendants any other relief that the Court deems just and proper.

CERTIFICATE OF SERVICE

I, Scott R. Jennette, do hereby certify that, I caused a copy of the foregoing document to be served upon the below-listed counsel of record via ECF on January 18, 2017, 2016, at the following addresses:

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